

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1-118. (Canceled)

119. (Currently amended) A ~~modified~~ GDF-8 propeptide that has been modified at the aspartate residue corresponding to Asp 76 of SEQ ID NO:5 comprising:

(a) — an amino acid sequence that is at least 75% identical 95% identical to SEQ ID NO:5, ~~or~~

(b) — ~~a fragment of the amino acid sequence of (a),~~

wherein the ~~modified GDF-8 propeptide~~ has modification is a mutation ~~that modifies the aspartate residue corresponding to Asp~~ at aspartate 76 of SEQ ID NO:5, and

wherein the ~~modified~~ GDF-8 propeptide has an increased in vivo or in vitro half-life relative to a corresponding unmodified GDF-8 propeptide; and

wherein the ~~modified~~ GDF-8 propeptide inhibits one or more GDF-8 activities chosen from GDF-8 propeptide binding, negative regulation of skeletal muscle mass, modulation of preadipocyte differentiation, inhibition of muscle formation, inhibition of muscle cell growth, inhibition of muscle development, regulation of muscle-specific enzymes, inhibition of myoblast cell proliferation, modulation of preadipocyte differentiation to adipocytes, increasing sensitivity to insulin, regulation of glucose uptake, glucose hemostasis, and modulation of neuronal cell development and maintenance.

120. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 119, wherein the residue corresponding to position 76 of SEQ ID NO:5 is alanine.
121. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 119 further comprising an Fc region of an IgG molecule.
122. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 121, wherein the IgG molecule is IgG1 or IgG4.
123. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 121, wherein the amino acid sequence of the IgG molecule is SEQ ID NO:16.
124. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 121, wherein the GDF-8 propeptide portion is fused to the Fc region of the IgG molecule via a linker peptide.
125. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 121, further comprising an altered glycosylation site.
126. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 121, further comprising at least one carbohydrate moiety.
127. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 119, further comprising albumin.
128. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 119, further comprising a nonproteinaceous polymer.
129. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 119, further comprising a second moiety.

130. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 129, wherein the second moiety is chosen from a protein, polypeptide, carbohydrate, and nonproteinaceous polymer.
131. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 119, wherein the ~~modified~~ GDF-8 propeptide further comprises an immunoglobulin molecule, or a fragment thereof.
132. (Currently amended) A pharmaceutical composition comprising the ~~modified~~ GDF-8 propeptide of claim 119 and a pharmaceutically acceptable excipient.
- 133-143. (Canceled)
144. (Currently amended) A ~~modified~~ GDF-8 propeptide that has been modified at the aspartate residue corresponding to ASP 76 of SEQ ID NO:5 comprising
- (a) —a GDF-8 moiety comprising
 - (i) —an amino acid sequence that is at least 75% identical 95% identical to SEQ ID NO:5 or
 - (ii) —~~a fragment of the amino acid sequence of (i), and~~
 - (b) ~~an optional heterologous moiety,~~
- wherein the GDF-8 moiety has a mutation in the amino acid sequence at the residue corresponding to position 76 of SEQ ID NO:5, and
- wherein the ~~modified GDF-8 propeptide has an increased~~ mutation increases the in vivo or in vitro half-life ~~relative to a corresponding unmodified of~~ the GDF-8 propeptide; and the
- ~~wherein the modified~~ GDF-8 propeptide inhibits one or more GDF-8 activities chosen from GDF-8 propeptide binding, negative regulation of skeletal

muscle mass, modulation of preadipocyte differentiation, inhibition of muscle formation, inhibition of muscle cell growth, inhibition of muscle development, regulation of muscle-specific enzymes, and inhibition of myoblast cell proliferation.

145. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the ~~mutation in the amino acid sequence at the residue corresponding to position 76 of SEQ ID NO:5 in the GDF-8 moiety~~ is a substitution mutation.
146. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 145, wherein the residue corresponding to position 76 of SEQ ID NO:5 is alanine.
147. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the GDF-8 moiety comprises an amino acid sequence that is at least ~~75% identical~~ 96% identical to SEQ ID NO:5.
148. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the GDF-8 moiety comprises an amino acid sequence that is at least ~~80% identical~~ 97% identical to SEQ ID NO:5.
149. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the GDF-8 moiety comprises an amino acid sequence that is at least ~~85% identical~~ 98% identical to SEQ ID NO:5.
150. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the GDF-8 moiety comprises an amino acid sequence that is at least ~~90% identical~~ 99% identical to SEQ ID NO:5.
151. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the GDF-8 moiety comprises an amino acid sequence ~~that is at least 95% identical to~~

~~SEQ ID NO:5~~ identical to SEQ ID NO:5, except that it has alanine at the residue corresponding to position 76 of SEQ ID NO: 5.

152. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the GDF-8 moiety comprises an amino acid sequence identical to SEQ ID NO:5, except that it has a mutation at the residue corresponding to position 76 of SEQ ID NO: 5.
- 153-159. (Canceled)
160. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the GDF-8 propeptide further comprises a heterologous moiety is-chosen from a protein, polypeptide, carbohydrate and nonproteinaceous polymer.
161. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 144, wherein the GDF-8 propeptide further comprises a heterologous moiety ~~comprises~~ comprising an immunoglobulin molecule, or a fragment thereof.
162. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 161, wherein the heterologous moiety comprises an Fc region of an IgG molecule.
163. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 162, wherein the IgG molecule is IgG1 or IgG4.
164. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 162, wherein the amino acid sequence of the IgG molecule is SEQ ID NO:16.
165. (Currently amended) A ~~modified~~ GDF-8 propeptide that has been modified at the aspartate residue corresponding to Asp 76 of SEQ ID NO:5 comprising
- (a)—an amino acid sequence that is at least 75%-identical 95% identical to SEQ ID NO:5, or-

~~(b) — a fragment of the amino acid sequence of (a), and~~

wherein the modified GDF-8 propeptide has an amino acid other than aspartate at the residue corresponding to position 76 of SEQ ID NO:5, and

wherein the modified GDF-8 propeptide has an increased in vivo or in vitro half-life relative to a corresponding unmodified GDF-8 propeptide; and

wherein the modified GDF-8 propeptide modulates one or more GDF-8 activities chosen from GDF-8 propeptide binding, negative regulation of skeletal muscle mass, modulation of preadipocyte differentiation, inhibition of muscle formation, inhibition of muscle cell growth, inhibition of muscle development, regulation of muscle-specific enzymes, inhibition of myoblast cell proliferation, modulation of preadipocyte differentiation to adipocytes, increasing sensitivity to insulin, regulation of glucose uptake, glucose hemostasis, and modulation of neuronal cell development and maintenance.

166. (Currently amended) The modified GDF-8 propeptide of claim 165, wherein the residue corresponding to position 76 of SEQ ID NO:5 is alanine.
167. (Currently amended) The modified GDF-8 propeptide of claim 165, wherein the modified GDF-8 propeptide further comprises an immunoglobulin molecule, or a fragment thereof.
168. (Currently amended) The modified GDF-8 propeptide of claim 165, wherein the modified GDF-8 propeptide further comprises an Fc region of an IgG molecule.
169. (Currently amended) The modified GDF-8 propeptide of claim 168, wherein the IgG molecule is IgG1 or IgG4.

170. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 168, wherein the amino acid sequence of the IgG molecule is SEQ ID NO:16.
171. (Currently amended) A ~~modified~~ GDF-8 propeptide that has been modified at the aspartate residue corresponding to Asp 76 of SEQ ID NO:5 comprising a non-human GDF-8 propeptide homolog of SEQ ID NO:5 chosen from bovine, dog, cat, chicken, murine, rat, porcine, ovine, turkey, baboon, and fish,
- wherein the ~~modified~~ GDF-8 propeptide has an amino acid other than aspartate at the residue corresponding to position 76 of SEQ ID NO:5, and
- wherein the ~~modified~~ GDF-8 propeptide has an increased in vivo or in vitro half-life ~~relative to a corresponding unmodified GDF-8 propeptide~~; and
- wherein the ~~modified~~ GDF-8 propeptide inhibits one or more GDF-8 activities chosen from GDF-8 propeptide binding, negative regulation of skeletal muscle mass, modulation of preadipocyte differentiation, inhibition of muscle formation, inhibition of muscle cell growth, inhibition of muscle development, regulation of muscle-specific enzymes, inhibition of myoblast cell proliferation, modulation of preadipocyte differentiation to adipocytes, increasing sensitivity to insulin, regulation of glucose uptake, glucose hemostasis, and modulation of neuronal cell development and maintenance.
172. (Currently amended) The ~~modified~~ GDF-8 propeptide of claim 119, wherein the mutation that modifies the aspartate residue corresponding to Asp 76 of SEQ ID NO:5 is chosen from a substitution, deletion, and insertion mutation.
173. (Currently amended) A ~~modified~~ GDF-8 propeptide that has been modified at the aspartate residue corresponding to Asp 76 of SEQ ID NO:5 comprising

(a) ~~an amino acid sequence that is at least 75% identical~~ 95% identical
to SEQ ID NO:5, ~~or~~

(b) ~~a fragment of the amino acid sequence of (a), and~~

wherein the ~~modified~~ GDF-8 propeptide has an amino acid other than
aspartate at the residue corresponding to position 76 of SEQ ID NO:5, and

wherein the ~~modified~~ GDF-8 propeptide inhibits a GDF-8 activity
associated with negative regulation of skeletal muscle mass and has an
increased in vivo or in vitro half-life relative to a corresponding unmodified GDF-8
propeptide.

174. (New) The GDF-8 propeptide of claim 173, wherein the propeptide has a substitution, insertion, or deletion in the amino acid sequence at the residue corresponding to position 76 of SEQ ID NO:5.
175. (New) The GDF-8 propeptide of claims 174, wherein the substitution, insertion, or deletion inactivates a proteolytic cleavage site.
176. (New) The GDF-8 propeptide of claim 173, wherein the propeptide has a substitution of the aspartate at the residue corresponding to position 76 of SEQ ID NO:5.
177. (New) The GDF-8 propeptide of claims 176, wherein the substitution, insertion, or deletion inactivates a proteolytic cleavage site.
178. (New) A GDF-8 propeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO:5, wherein the GDF-8 propeptide has a mutation at aspartate 76 of SEQ ID NO:5, wherein the mutation increases the in vivo or in

vitro half-life of the GDF-8 propeptide, and wherein the GDF-8 propeptide inhibits a GDF-8 activity associated with negative regulation of skeletal muscle mass.

179. (New) The GDF-8 propeptide of claim 178, wherein the mutation is a substitution, insertion, or deletion mutation.
180. (New) The GDF-8 propeptide of claims 178, wherein the mutation inactivates a proteolytic cleavage site.
181. (New) The GDF-8 propeptide of claim 178, wherein the mutation is a substitution of the aspartate at the residue corresponding to position 76 of SEQ ID NO:5.
182. (New) The GDF-8 propeptide of claims 181, wherein the mutation inactivates a proteolytic cleavage site.